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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JACQUES ALEXANDRE HATZFELD and
ANTOINETTE HATZFELD

Appeal 2008-6239
Application 09/980,484
Technology Center 1600

Decided: [1] February 12, 2009

Before DONALD E. ADAMS, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

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[1] The two-month time period for filing an appeal or commencing a civil action, as provided for in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

DECISION ON APPEAL

This is a decision on appeal from the Examiner's final rejection of claims 1, 8, 9, 11, and 33-36. Jurisdiction for this appeal is under 35 U.S.C. § 6(b). The Examiner's final rejection is affirmed-in-part.

STATEMENT OF THE CASE

The claims are directed to a method for multiplying stem cells while maintaining the cells in a non-differentiated state. Claims 1 and 33 are the only independent claims on appeal. Each of the claims involves sequentially administering TGFβ ("transforming growth factor") and anti-TGFβ to human stem cells. TGFβ was known to inhibit stem cell proliferation and differentiation (Spec. 2:10-15). Anti-TGFβ neutralizes the activity of the TGFβ, allowing the stem cells to leave the resting state and begin dividing (Spec. 6:15-16).

Claims 1, 8, 9, 11, and 33-36 stand rejected by the Examiner under 35 U.S.C. § 103(a) as obvious over Hatzfeld (*Stem Cell Cycling: From Theory To Cell Therapy,* 25 EXP. HEMATOLOGY 777 (Abstract 174), 1997) and Fortunel (*High Proliferative Potential-Quiescent cells: a working model to study primitive quiescent hematopoietic cells,* 111 J. OF CELL SCIENCE 1867-1875, 1998) (Ans. 3). Claims 1 and 33 are representative and read as follows:

> 1. A method for maintaining a non-differentiated state of human stem cells, while allowing cell division of said human stem cells, comprising
>
> administering to said human stem cells an effective amount of an inhibitor of cell development in sequential combination with an anti-inhibitor of cell proliferation in a controlled manner to maintain the non-differentiated state of stem cells, while allowing their cell division until the

amplification of the cells is sufficient to obtain a pre-determined number of cells,

wherein said anti-inhibitor is anti-TGFβ in an amount of 10^{-18} mg/ml to 10 mg/ml, and wherein said inhibitor is TGFβ in an amount of 0.01 pg/ml to 1 mg/ml and said human stem cells are hematopoietic stem cells.

33. A method for maintaining a non-differentiated state of human stem cells, while allowing cell division of said human stem cells, comprising

repeatedly administering to human stem cells in a cell concentration of about 1 to about 10^{10} cells per ml an effective amount of an inhibitor of cell proliferation of cell development in sequential combination with an anti-inhibitor in a controlled manner to maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells is sufficient to obtain a predetermined number of cells,

wherein said anti-inhibitor is anti-TGFβ in an amount of 0.1 μg to 10 mg/ml, and wherein said inhibitor is TGFβ in an amount of 0.01 pg/ml to 1 mg/ml and said human stem cells are hematopoietic stem cells.

ISSUES ON APPEAL

Does Hatzfeld describe a method comprising administering to stem cells a sequential combination of TGFβ and anti-TGFβ that "maintain[s] the non-differentiated state of stem cells, while allowing their cell division" as recited in claims 1 and 33?

Do Hatzfeld and Fortunel suggest administering the sequential combination of TGFβ and anti-TGFβ more than once ("repeatedly") to stem cells as in claim 33?

PRINCIPLES OF LAW

To establish obviousness, the following factors must be taken into consideration: (a) the scope and contents of the prior art; (b) the differences

between the prior art and the claimed subject matter; (c) the level of skill in the pertinent art; and (d) evidence of secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

Factual findings on obviousness include findings on: "1) the reason, suggestion, or motivation present in the prior art, in the knowledge of those of ordinary skill in the art, or in the problem [to be solved] which clearly and particularly would lead one of ordinary skill in the art to combine [the prior art]; [and] 2) the level of ordinary skill in the art." *Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 660 (Fed. Cir. 2000).

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on "inherency" under 35 U.S.C. § 102, on "prima facie obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1255 (CCPA 1977) (footnote omitted).

"[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

FINDINGS OF FACT (FF)

Scope and content of the prior art

Hatzfeld

1. In vivo, stem cells (hematopoietic progenitors) are maintained in a quiescent (resting, not dividing) state (Hatzfeld).

2. Hatzfeld states that endogenous or "added" TGFβ down modulates cytokine receptors on stem cells and inhibits their proliferation (Hatzfeld; *see* Ans. 3).

3. Hatzfeld teaches that TGFβ's effect on stem cells can be suppressed or neutralized by anti-TGFβ antibodies (Hatzfeld; *see* Ans. 3-4).

4. An assay is described by Hatzfeld called "High Proliferative Potential-Quiescent progenitors (HPP-Q assay)." This assay involves the addition of anti-TGFβ together with cytokines to cause in vitro expansion of stem cells, releasing the cells from growth inhibition produced by endogenous or "added" TGFβ (*id.*; *see also* Fortunel ("SUMMARY"); *see* Ans. 3-4).

5. Hatzfeld does not teach the repeated addition of both TGFβ and anti-TGFβ antibodies to stem cells.

Fortunel

6. Fortunel is cumulative to Hatzfeld's teaching that TGFβ inhibits stem cell growth and that blocking TGFβ with anti-TGFβ antibodies in the presence of cytokines activates the cells, initiating their growth (Fortunel, at 1867) ("We have previous demonstrated that blocking [TGFβ] . . . [with anti-TGFβ] is able to activate, in the presence of cytokines" quiescent hematopoietic stem cells.)

7. Fortunel states:

> When a quiescent stem/progenitor cell is activated, it maintains for a few divisions its immature phenotype and its high proliferative potential. . . . Similarly, we have evidence that even after activation, HPP-Q cells maintain for at least one division their ability to return to a quiescent state in response to physiological concentrations of TGF-β1.

(Fortunel, at 1872, col. 2; quoted on pages 6-7 of Answer.)

8. Fortunel does not teach the repeated addition of both TGFβ and anti-TGFβ antibodies to stem cells.

Differences between the claim 1 and the prior art

9. Claim 1 is directed to a method "for maintaining a non-differentiated state of human stem cells, while allowing cell division."

10. The method involves administering to hematopoietic stem cells:

11. TGFβ ("an inhibitor of cell development") and

12. anti-TGFβ ("an anti-inhibitor of cell proliferation").

13. The TGFβ and anti-TGFβ are administered in "sequential combination."

14. The phrase "sequential combination" is defined in the Specification to mean "that the anti-inhibitor of cell proliferation is not used simultaneously with the inhibitor of cell development" (Spec. 4:2-3). In other words, the TGFβ and anti-TGFβ are administered one at a time.

15. The combination is administered "in a controlled manner to maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells is sufficient to obtain a pre-determined number of cells." (Claim 1.)

16. The claims recite administration of TGFβ and anti-TGFβ in specific amounts.

17. Hatzfeld describes administering TGFβ ("added TGF-β") to hematopoietic stem cells (FF1, 2) as required by claim 1 (FF10, 11; Ans. 3).

18. Hatzfeld describes administering anti-TGFβ antibodies to the cells (FF3) as in the claim (FF10, 12; Ans. 3).

19. The anti-TGFβ is provided after the TGFβ to block the latter's effect (FF3) and therefore each is administered one at a time (FF14), meeting the limitation of claim 1 of "administering . . . in sequential combination" (Ans. 6-7).

20. Hatzfeld does not describe the amounts of TGFβ and anti-TGFβ recited in the claims, but Appellants do not dispute the Examiner's finding (Ans. 4) that Fortunel teaches concentrations of each which fall within the claimed amounts.

21. Neither Hatzfeld nor Fortunel expressly state that the claimed sequential combination of TGFβ and anti-TGFβ "maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells is sufficient to obtain a pre-determined number of cells" (claim 1).

22. However, based on Fortunel's teaching that anti-TGFβ activates non-dividing stem cells and causes them to proliferate while maintaining "for a few divisions its immature phenotype"[2] (FF6, 7), the Examiner found that the claim limitation would inherently be met when the steps of sequentially administering TGFβ and anti-TGFβ, as in Hatzfeld's HPP-Q method, were accomplished (*see* Ans. 6-7; FF17, 18).

[2] The Examiner interpreted "immature phenotype" to mean claimed "nondifferentiated state of stem cells."

Differences between claim 33 and the prior art

23. Claim 33, as with claim 1, is directed to a method "for maintaining a non-differentiated state of human stem cells, while allowing cell division" involving the administration of a "sequential combination" of TGFβ and anti-TGFβ "in a controlled manner to maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells is sufficient to obtain a pre-determined number of cells."

24. The "sequential combination" is "repeatedly" administered to the stem cells. We interpret "repeatedly" to mean that the combination is administered more than once to the stem cells.

25. Claim 33 also recites specific amounts of the TGFβ and anti-TGFβ.

26. As for claim 1, Hatzfeld describes all the limitations of claim 33 (*see* FF17-20), but not the "repeated" administration of the sequential combination of TGFβ and anti-TGFβ.

27. Neither Hatzfeld nor Fortunel expressly states that the claimed sequential combination of TGFβ and anti-TGFβ "maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells is sufficient to obtain a pre-determined number of cells" (claim 33). However, based on their combined teachings, the Examiner found that the claim limitation would inherently be met when the steps of sequentially administering TGFβ and anti-TGFβ, as taught in Hatzfeld's HPP-Q method, were accomplished (*see* Ans. 6-7).

ANALYSIS

Claim 1

Independent claim 1 is to a method "for maintaining a non-differentiated state of human stem cells, while allowing cell division" involving administration of specific amount of a "sequential combination" of TGFβ and anti-TGFβ. Hatzfeld describes all the limitations of the claimed method, but does not teach the specific amounts of TGFβ and anti-TGFβ (FF17-19). However, the Examiner finds that these amounts are suggested by Fortunel (FF20). Appellants do not appear to dispute this finding.

Appellants contend that neither Hatzfeld nor Fortunel suggest administering the claimed sequential combination "in a controlled manner to maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells" (*see* App. Br. 4-5). Rather, Appellants urge that Hatzfeld "actually leads one skilled in the art away from the claimed invention" because it teaches "pushing the cells towards further differentiation instead of maintaining them in a non-differentiated state" (*id.* at 5).

This argument does not persuade us that the Examiner erred. As pointed out by the Examiner, Fortunel teaches that anti-TGF-β maintains the progenitor's "immature phenotype" for at least one cell division (FF7). The Examiner understood "immature phenotype" to mean "the non-differentiated state of stem cells." As this is a reasonable inference, and Appellants have not proffered any evidence that the Examiner's inference is flawed, we adopt it as our own. Thus, even were it true that the cells were subsequently pushed to "further differentiation" (App. Br. 4-5), Fortunel would be reasonably understood to teach that after the addition of TGFβ, then its

neutralization with anti-TGFβ, the cells would be maintained in "the non-differentiated state of stem cells ["immature phenotype"]," while "allowing their cell division" for at least one cell division, satisfying the limitation of claim 1.

Appellants argue that the Examiner inappropriately stated that the claimed limitation "would necessarily occur as a result of the 'combined art' (see Examiner's Answer, page 4, last three lines). Indeed, [n]either publication discloses such features" (Reply Br. 6).

This argument is also not persuasive. The PTO does not have the ability "to manufacture products or to obtain and compare prior art products." *In re Best*, 562 F.2d at 1255. Thus, once sound basis is provided for believing that the prior art accomplishes the same result which is claimed, the burden properly shifts to the applicant to show it does not. *See In re Spada*, 911 F.2d at 708. In this case, Hatzfeld describes a method which comprises the same steps of claim 1 in which a sequential combination of TGFβ and anti-TGFβ is administered to hematopoietic stem cells (FF17-19). Based on these similarities and other factual findings, the Examiner had logical, fact-based reasons (F21, 22) for believing that Hatzfeld combined with Fortunel "maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells is sufficient to obtain a pre-determined number of cells" as recited in claim 1. Appellants have not provided sufficient arguments or evidence to rebut the grounds on which the reasonable belief was based.

Appellants assert in their briefs that neither Hatzfeld nor Fortunel teach administering TGFβ and anti-TGFβ as a sequential combination (App. Br. 6-7; Reply Br. 5). We do not agree. The Examiner made specific

findings, with which we agree, about Hatzfeld's teaching (summarized in FF1-5; Ans. 3-4). Appellants have not identified a deficiency in these findings nor in Hatzfeld.

For the foregoing reasons, we affirm the rejection of claim 1.

Claim 33

Claim 33 is directed to the same method of claim 1, but further requires "repeatedly administering to human stem cells" a sequential combination of TGF-β and anti-TGF-β. We agree with Appellants that this additional limitation is neither disclosed nor suggested by the combination of Hatzfeld and Fortunel or either reference alone.

The closest disclosure is Fortunel's statement that "even after activation, HPP-Q cells maintain for at least one division their ability to return to a quiescent state in response to physiological concentrations of TGF-β1" (FF7). Assuming that activation is by anti-TGFβ which is preceded by TGFβ as in Hatzfeld's method (FF2, 3), then Fortunel teaches administering another round of TGFβ to show that the cells do not lose their sensitivity to it (FF7). However, the Examiner has not provided a reason as to why persons of ordinary skill in the art would have re-administered anti-TGFβ after the second dose of TGFβ. The TGFβ is administered again apparently to show that the cells are still TGFβ responsive (FF7; "maintain for at least one division their ability to return to a quiescent state in response to physiological concentrations of TGF-β1"). We agree with Appellants that this teaching does not "suggest that it would be beneficial to repeatedly" administer the sequential combination (Reply Br. 5). The second round of TGFβ was for the purpose of testing the properties of the activated cells and

thus represents an endpoint of Fortunel's experiment. The Examiner has not provided a reason as to why anti-TGF would be administered again for a second time.

We reverse the rejection of claim 33 and dependent claims 34-36 which depend on claim 33 and incorporate all its limitations.

CONCLUSIONS OF LAW

Hatzfeld describes a method comprising administering to stem cells a sequential combination of TGFβ and anti-TGFβ that "maintain[s] the non-differentiated state of stem cells, while allowing their cell division" as recited in claim 1. We therefore affirm the obviousness rejection of claim 1. Claims 8, 9, and 11 depend on claim 1 and incorporate all its limitations. As these claims were not separately argued, we affirm their rejection as well. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Hatzfeld in combination with Fortunel does not suggest "repeatedly" administering the sequential combination of TGFβ and anti-TGFβ to stem cells as in claim 33. The obviousness rejection of claim 33 and dependent claims 34-36 is reversed.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

cdc

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